Scientific Abstract.

Our group has focused on the development and application of chimeric immunoglobulin-T cell receptors (IgTCR) for cancer therapy. These molecules are fusion products of the antibody (Ab) binding domain with the ζ signaling chain of the TCR. When expressed by gene therapy techniques in recipient T cells, the resulting "designer T cells" are redirected by the IgTCR neo-specificity to attack tumors expressing the surface antigen (Ag) recognized by the Ab. This combines the specificity of Ab against CEA with the cytotoxic potency of T cells in a new type of immune therapy against colorectal cancer. This strategy is designed to bypass a major drawback of cancer immunotherapy approaches, which have been hampered by the fact that most "tumor antigens" are normal self-proteins to which the patient is already tolerized. We performed a phase I clinical trial with 1st generation (1st gen) designer T cells that generate Signal 1 (TCR) on tumor contact. Autologous patient T cells were transduced and expanded ex vivo then administered in a dose escalation plan to 10^{11} cells. This study yielded preliminary indications of efficacy but with limited duration of response. In vitro correlates suggested that activation induced cell death (AICD) contributed to lack of in vivo persistence of the infused T cells. This prompted a redesign to add CD28 co-stimulation (Signal 2) on tumor contact via an IgCD28TCR. These 2nd generation designer T cells with Signal 1+2 were shown to overcome AICD and instead undergo accelerated proliferation on contact with CEA+ tumor targets with sustained tumoricidal activity. Such cells also displayed enhanced IL2 and γ-interferon secretion. The general plan is to perform genetic modification of patient T cells by ex vivo gene transduction to create a neo-specificity directed at tumor-associated CEA in a phase I dose escalation. Patient T cells are infected with retrovirus containing anti-CEA IgCD28TCR to create the 2nd gen designer T cells. These cells are returned to the patient by intravenous administration, and the patient is followed for toxicity and response.